REMARKS

This responds to the May 16, 2005 Office Action that was received from the United States Patent and Trademark Office in connection with in the above-identified application.

Claims 42-43, 45-51, 53, 55-56, 82 and 85-88 are pending.

Applicants have amended claim 42 to more particularly point out the subject matter applicants view as the invention. Support for the amendments is found, *e.g.*, on page 7, line 28 to page 8, line 6 of the specification as filed.

Applicants have amended claim 48 to recite, in the "transfecting" paragraph, the limitations of claim 42. Applicants have further amended claim 48 to delete the phrase "said carboxy terminal portion of the heavy chain of botulinum neurotoxin serotype B" and replace it with the phrase "the polypeptide comprising the amino acid sequence of SEQ ID NO:8." Applicants have also amended the "wherein" paragraph to recite a "gram negative bacterium, a yeast cell, and cell of a mammalian cell line." Support for the above amendments is found, *e.g.*, on page 7, lines 1-14 and page 7, line 28 to page 8, line 6 of the specification as filed.

Applicants have amended claim 53 to recite, in the "culturing" paragraph, the limitations of claim 42. Applicants have further amended the "wherein" paragraph to recite a "gram negative bacterium, a yeast cell, and cell of a mammalian cell line." Support for the above amendments is found, *e.g.*, on page 7, line 28 to page 8, line 6 of the specification as filed.

Applicants have amended claim 82 to delete "recombinant." Support for the amendment is found, *e.g.*, on page 15, line 20 to page 16, line 1, of the specification as filed.

Applicants have added new claims 87 and 88, drawn to a synthetic nucleic acid sequence of SEQ ID NO:7. Support for the claims is found, *e.g.*, on page 7, line 1 to page 8, line 6; page 13, line 28 to page 15, line 12.

Applicants respectfully request entry of the amendments, which are supported by the application and, therefore, do not constitute new matter.

The Objections

The Examiner has objected to claim 48 for allegedly being confusing. The Examiner asserts that the "transfecting" paragraph in claim 48 utilizes a nucleic acid that encodes a polypeptide of SEQ ID NO:8 but expresses polypeptides that have amino acid sequences other than SEQ ID NO:8, in light of claim 49 defining the sequence to be SEQ ID NO:8. The Examiner further alleges that claim 49 is not further limiting of claim 48 in light of applicant's prior amendment to remove the phrase "having at least one immunogenic epitope." Applicants amend in part and traverse in part.

In response, as suggested by the Examiner, Applicants have amended claim 48 to recite, in the "culturing" paragraph, that the nucleic acid is expressed and "the polypeptide comprising the amino acid sequence of SEQ ID NO:8 is produced."

Applicants respectfully assert that claim 49 further limits claim 48. Claim 48 provides for a method of preparing a polypeptide comprising a carboxy-terminal portion of the heavy chain of botulinum neurotoxin serotype B, comprising two steps: transfecting a cell with a nucleic acid encoding a polypeptide comprising the amino acid sequence of SEQ ID NO:8, and culturing the cell so that the nucleic acid is expressed and a polypeptide having the amino acid sequence of SEQ ID NO:8 is produced. Claim 49 provides for a *third* step:

recovering from the cell the produced polypeptide having the amino acid sequence of SEQ ID NO:8. Thus, in view of the amendment and remarks, Applicants respectfully request the objections to claim 48 and 49 be withdrawn.

The Examiner has objected to claim 53, alleging that the recitation of the term "mammalian cell" in the claim is inconsistent with the recitation of "mammalian cell lines" in the instant specification. Applicants have amended claim 53 to recite "a cell of a mammalian cell line." Accordingly, in view of the amendment, Applicants request that the objection to claim 53 be withdrawn.

The Examiner has objected to claim 82, alleging that the recitation of the phrase "a recombinant host cell" is confusing because it could refer to cells that recombine in nature. Applicants respectfully traverse. Applicants assert that a skilled artisan would recognize that a "recombinant host cell" is a cell that has been genetically manipulated in vitro to express a particular nucleic acid sequence. Moreover, applicants have amended claim 42 (from which claim 82 ultimately depends) to require that the nucleic acid of interest is produced by genetic engineering and, as such, is constructed experimentally and does not exist in nature. Thus, a "recombinant host cell" comprising a recombinant nucleic acid would not refer to cells that recombine in nature. These reasons notwithstanding, to advance prosecution, Applicants have deleted "recombinant" from claim 82, so that the objection should be removed.

The Written Description Rejection Under 35 U.S.C. §112, 1st Paragraph

The Examiner has rejected claims 42-43, 45-51, 53, 55-56, 82, and 85-86 under 35 U.S.C. §112, 1st paragraph, as allegedly containing subject matter not adequately described in

the specification so as to convey to one of skill in the art that, at the time of filing, the inventors possessed the claimed invention. The Examiner alleges that Applicants' specification broadly describes isolated polynucleotides encoding the polypeptide comprising SEQ ID NO:8; botulinum neurotoxin Hc fragments encoded by the polynucleotide sequence of SEQ ID NO:7; and polynucleotides encoding the polypeptide of SEQ ID NO:8, and includes continuous or discontinuous regions encoding the polypeptide as well as coding and noncoding regions associated with the expression vector sequences. The Examiner alleges that the claims encompass polynucleotide sequences comprising SEQ ID NO:7, nucleotides 10-1332, sequences that have a recited degree of change as compared to SEQ ID NO:7, nucleotides 10-1332, and comprising nucleic acid encoding SEQ ID NO: 8. The Examiner alleges that none of these sequences meets the written description requirement of 35 U.S.C. §112, 1st paragraph.

Rather, the Examiner alleges that the specification only discloses a polynucleotide consisting of SEQ ID NO:7 encoding a polypeptide of SEQ ID NO:8, an isolated nucleic acid consisting of SEQ ID NO:7 and an isolated amino acid sequenced consisting of SEQ ID NO:8 but, for example, not vectors comprising SEQ ID NO:7, host cells and methods of producing the polypeptide of SEQ ID NO:8. In short, the Examiner alleges that the written description does not provide for an "operon" that discloses the "synthetic botulinum neurotoxin serotype B" gene. As a result, the Examiner contends that the skilled artisan cannot envision all the contemplated nucleotide sequences by the detailed chemical structure of the claimed nucleic acid sequences, and so conception cannot be achieved until reduction to practice has occurred. The Examiner has indicated that claims directed to an isolated nucleic acid encoding a fusion protein comprising a polynucleotide encoding the amino acid sequence consisting of SEQ ID NO: 8 may overcome this rejection. Applicants traverse in part and amend in part.

Applicants respectfully assert that the claims, as amended, are adequately described in and fully supported by the specification and convey to one of skill in the art that, at the time of filing, the inventors possessed the invention. As amended, claim 42 specifies a nucleic acid sequence encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 8, wherein said nucleic acid sequence is obtained by genetic engineering and designed by selecting at least a portion of the codons of said nucleic acid sequence from codons preferred for expression in a host organism. Applicants further provide detailed written description of the design and construction of SEQ ID NO: 7 as well as, for example, insertion thereof into an expression vector and integration into the chromosome of *Picha pastoris*. *See*, page 16, line 22 to page 17, line 2; page 38, line 4 to page 39, line 32.

Applicants are not required to provide full support for a reconstructed bacterial operon. The purpose of the invention is to provide sufficient amounts of non-toxic, immunogenic protein to be used as a vaccine against botulinum toxin. The person skilled in the art, armed with a nucleic acid encoding the nontoxic, immunogenic protein, would know how to create a suitable nucleic acid construct and to insert the construct into a suitable host cell, to result in protein expression.

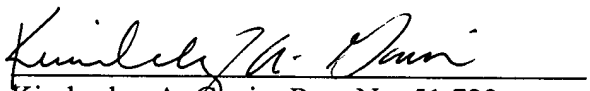
In view of the amendments and remarks made herein, applicants respectfully request that the rejection of claims 42-43, 45-51, 53, 55-56, 82, and 85-86 under 35 U.S.C. § 112, first paragraph, be withdrawn.

Conclusion

Applicants believe that the claims, as amended herein, are in condition for allowance and respectfully and earnestly request a favorable action thereon.

Applicants believe that no additional fee is due in connection with the filing of this response. However, if any fee is due or overpayment made with regard to this communication, the Director is hereby authorized, in the accompanying Transmittal Form (submitted in duplicate), to charge any such fee, and to credit any overpayment, to Deposit Account No. 02-4377.

Respectfully submitted,



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